Reversal of the Cardiovascular Effects of Verapamil by Calcium and Sodium: Differences Between Electrophysiologic and Hemodynamic Responses

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SUMMARY: The reversibility of verapamil-induced hemodynamic and electrophysiologic changes by intravenously administered CaCl₂ and NaCl was tested in 34 anesthetized open-chest dogs during verapamil infusions which produced plasma verapamil concentrations of 70–2042 ng/ml. An increase of serum calcium concentration (Ca₄₉₀) to an average 6.5 mEq/l abolished the depressive effects of verapamil on cardiac output and left ventricular dp/dt and diminished drug-related hypotension by an average of 52%, but did not affect verapamil-induced prolongation of AH interval and slowing of sinus rate. Further increase of (Ca₄₉₀) to an average of 8.2 mEq/l decreased AH prolongation caused by verapamil from an average of 95% to 45% of control value, but had no effect on verapamil-induced slowing of sinus rate or second-degree atrioventricular (AV) block during atrial pacing. Rapid intravenous injection of 40 ml 2 M NaCl, transiently raised serum Na⁺ concentration to 162 mEq/l, decreased AH prolongation caused by verapamil to an average of 22% of control value, decreased slowing of sinus rate from an average of 34% to an average of 19% of control value, and decreased the severity of second-degree AV block, but had no effect on verapamil-induced complete AV block or sinus arrest. Hypernatremia had no effect on AH interval and sinus rate without prior CaCl₂ infusion. In the absence of verapamil, neither increase of (Ca₄₉₀) to 8.2 mEq/l, nor NaCl injection following CaCl₂ had any effect on AH interval or sinus rate. This study suggests 1) that both Ca⁺⁺ and Na⁺ compete with verapamil, but Na⁺ acts only in the presence of hypercalcemia; 2) different verapamil effects differ in their reversibility; and 3) treatment with calcium may be useful in countering the negative inotropic effect of verapamil.

VERAPAMIL BLOCKS the slow inward membrane current carried primarily by calcium, but also by sodium ions.1-3 This current is believed to be an important factor in the depolarization of the sinoatrial (SA) and atrioventricular (AV) nodes4-7 and in excitation-contraction coupling in the myocardium.1,8 Verapamil is useful in terminating reentrant supraventricular tachycardia and in slowing ventricular rate in atrial fibrillation or flutter.8,9 However, it can cause AV block, sinus bradycardia, depression of myocardial contractility and hypotension.10

Previous studies have shown the Ca⁺⁺ added to a tissue bath reversed the suppressive effects of verapamil on the membrane current flowing through the slow channel,2 on the slow channel-dependent automaticity in guinea pig myocardium,12 and on the contractility in the mammalian myocardium at slow heart rates.5 In vivo, Ca⁺⁺ reversed the suppressive effect of verapamil on digitalis-induced arrhythmias in dogs.13 Similarly, an increase in extracellular Na⁺ concentration abolished the verapamil-induced second-degree AV block and restored 1:1 conduction in the isolated rabbit heart.14

Verapamil concentration in the body fluids has not been measured in any of the previous studies. In our laboratory, M'Callister et al. have developed an assay for verapamil in plasma,15 studied the elimination kinetics of the drug in dogs,16 and designed intravenous bolus-infusion regimens that enabled us to correlate various plasma verapamil concentrations with the cardiovascular effects of the drug.11 In this paper we report the reversibility of these effects in vivo by CaCl₂ and NaCl administration, at different plasma verapamil concentrations.17,18

Materials and Methods

We studied 34 open-chest dogs (17–25 kg), anesthetized with sodium pentothal (30 mg/kg i.v.) and mechanically ventilated using a respirator. Serial determinations of arterial pH, Pco₂, and Po₂ at 30-minute intervals were done to insure adequate ventilation. The methods of measuring hemodynamic parameters — cardiac output, dp/dt of the left ventricular pressure, aortic blood pressure, and peripheral vascular resistance, and the electrophysiologic parameters (AH interval and AV nodal refractory periods) — were described in our previous paper.11 These
parameters were measured during atrial pacing at a constant rate and, except for the AV nodal refractory periods, were expressed as an average value of five complexes. His bundle pacing was used when second- or third-degree AV block developed. Throughout all experiments, pacing rate was constant, and the driving rate was the slowest required to suppress the spontaneous rhythm, usually about 2.5 Hz. PP interval was determined as an average value of 10 consecutive spontaneous complexes.

Verapamil (Knoll Pharmaceutical Co) was administered according to bolus-infusion method, where each bolus was given at a rate of 3 mg/min. Ten dogs received 3.0–4.2 mg bolus followed by constant infusion at 0.06 mg/min; 11 dogs received 7.0–8.5 mg bolus followed by constant infusion at 0.15 mg/min; and three dogs received 14.0–21.5 mg bolus followed by infusion at 0.33 mg/min. In two dogs, verapamil was given in excess of the above doses to produce plasma concentrations of about 1000 and 2000 ng/ml.

We studied the effects of increased serum calcium* and/or sodium serum concentrations in those 26 verapamil-treated dogs and in eight control dogs not treated with verapamil. In eight of the verapamil-treated dogs, we monitored all hemodynamic and electrophysiologic parameters simultaneously, and in the other 18 dogs, only the electrophysiologic parameters and the arterial pressure. In those eight dogs, 10% CaCl₂ solution was infused at a rate of 3 mg/kg/min for 15 minutes, while the rate of verapamil infusion was unchanged. In 13 of the 18 dogs, similar CaCl₂ infusion was followed by three successive intravenous injections made at 5-minute intervals in the following order: first, 40 ml of 2 M NaCl solution; then 40 ml of 2 M Na lactate solution; finally, 40 ml of 2 M sucrose solution. In the other five of the 18 dogs a similar NaCl injection preceded the CaCl₂ infusion by an interval of 15 minutes; this infusion was again followed by similar injections of NaCl, Na lactate and sucrose.

The same method of administration of calcium and sodium salt solutions was used in the eight control dogs. Of these, four received CaCl₂ infusion at a rate of 3 mg/kg/min for 60 minutes; and the other four, one NaCl injection, followed 15 minutes later by 15 minutes of CaCl₂ infusion 3 mg/kg/min, and then three successive injections of NaCl, Na lactate and sucrose at 5-minute intervals.

Results

Plasma Verapamil, Calcium and Sodium Concentrations

In each experiment, plasma verapamil concentrations measured immediately before and after completion of CaCl₂, NaCl, Na lactate, and sucrose infusions did not differ from each other by more than 15%.

Serum calcium concentrations (Caₐ) increased from an average control value of 4.6 ± 0.2 mEq/l to an average of 6.5 ± 0.2 mEq/l after 5 minutes, and to an average of 8.2 ± 0.3 mEq/l after 15 minutes of CaCl₂ infusion. The latter concentrations did not change by more than 1.0 mEq/l at the time of the subsequent sodium salt and sucrose injections.

Figure 1. Effects of verapamil alone, after CaCl₂, and after CaCl₂ + NaCl administration on the percent change of AH interval from control. Vertical bars are the average values and the vertical lines at their tops, the mean ± SEM. The numbers of dogs (N) are shown under each bar. Statistical significance of p₁ relates to the comparison between values in the first bar, vs those in the other bars. Statistical significance of p₂ is a comparison of values in the third vs those in the fourth bar. Serum calcium concentrations (mean ± SEM) from left to right are: 4.6 ± 0.2, 6.6 ± 0.2, 8.2 ± 0.2, and 8.0 ± 0.3 mEq/l.

AH Intervals in Verapamil-treated Dogs

The results are summarized in figure 1, which shows the mean (± SEM) AH intervals during atrial pacing at plasma verapamil concentrations varying from 70–377 ng/ml. The AH interval increased after verapamil administration by an average of 95% and did not change significantly at an average (Caₐ) of 6.5 mEq/l, i.e., after 5 minutes of CaCl₂ infusion. However, at (Caₐ) averaging 8.2 mEq/l, i.e., after 15 minutes of CaCl₂ infusion, AH interval shortened significantly, reaching a value that was about 45% longer than the control AH interval. Injections of NaCl during sustained hypercalcemia produced further shortening of AH interval to an average value which was still 22% longer than the control AH interval.

In all experiments, the effects of CaCl₂ on the AH interval persisted for at least 45 minutes after the end of calcium infusion, even though the verapamil administration was continued. However, the effect of NaCl injection lasted only about 1 minute. The NaCl-induced shortening of AH interval during hypercalcemia could be reproduced by repeated injections.

*We assume that the fraction of ionized calcium was constant in our experiments because blood pH was kept constant and plasma proteins were not expected to change.
of NaCl or Na lactate. In this group of six dogs, changes induced by second injection of NaCl or by injection of Na lactate after NaCl did not differ significantly from those induced by the first injection of NaCl.

The effects of NaCl and Na lactate were not due to change in osmolality, because an iso-osmolar sucrose solution had no effect on the AH interval. Rapid administration of larger than 40-ml volumes of NaCl, Na lactate, or sucrose solutions caused atrial fibrillation.

NaCl injections not preceded by CaCl₂ infusions had no significant effect on the AH interval in four dogs at plasma verapamil concentrations varying from 100–270 ng/ml. In these animals, verapamil-induced AH prolongation averaged 67 ± 15% of control value before and 63 ± 18% of control value after NaCl injection.

AH Intervals in Dogs Not Treated with Verapamil

Administration of NaCl had no effect on the AH intervals before or after CaCl₂ infusions. In the four control dogs, AH interval averaged 85 ± 8 msec before administration of sodium and calcium salts, 82 ± 12 msec after the first NaCl injection, 80 ± 10 msec after 15 minutes of CaCl₂ infusion and 86 ± 13 msec SEM after the repeated NaCl injection. The differences between these values were not significant. Administration of CaCl₂ for 15 minutes did not change the AH interval, but longer duration of infusion associated with higher serum calcium concentrations increased the AH interval. Figure 2 shows an experiment in which the increase of AH interval occurred when (Ca)ₙ reached 9.6 mEq/l. In the other three dogs, the onset of AH prolongation occurred at (Ca)ₙ 9.4 mEq/l, 10.9 mEq/l, and 11.0 mEq/l.

AV Nodal Effective and Functional Refractory Periods, Second and More Advanced Degrees of AV Block in Verapamil-treated Dogs

The effects of CaCl₂ infusion on the AV nodal refractory periods paralleled those on the AH interval. The verapamil-induced prolongation of the AV nodal effective and functional refractory periods was partly reversed after 15 minutes of CaCl₂ infusion. Figure 3 shows a representative experiment in which verapamil increased the effective refractory period from 140 to 315 msec, and the functional refractory period from 230 to 400 msec. After 15 minutes of CaCl₂ infusion which increased (Ca)ₙ from 4.6 to 7.9.
Table 1. Effect of a 15-minute CaCl₂ Infusion (45 mg/kg) and a Rapid I.V. 40 ml 2 M NaCl Injection to Verapamil-induced Second-degree Atrioventricular Block

<table>
<thead>
<tr>
<th>Dog</th>
<th>[V] (ng/ml)</th>
<th>Atrioventricular block</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>455</td>
<td>V + Ca = 4.3</td>
</tr>
<tr>
<td>2</td>
<td>480</td>
<td>V + Ca = 2:1</td>
</tr>
<tr>
<td>3</td>
<td>262</td>
<td>V + Ca = 2:1</td>
</tr>
<tr>
<td>4</td>
<td>315</td>
<td>V + Ca = 2:1</td>
</tr>
<tr>
<td>5</td>
<td>272</td>
<td>V + Ca = 2:1</td>
</tr>
</tbody>
</table>

Abbreviations: [V] = plasma verapamil concentrations; V = after verapamil administration; V + Ca = after a 15 minute CaCl₂ infusion; V + Ca + Na = after a rapid injection of NaCl.

In five dogs, second-degree AV block occurred at plasma verapamil concentrations from 262-480 ng/ml. In these animals, CaCl₂ infusion of 15 minutes duration did not change the AV block, but the number of conducted complexes increased when NaCl was injected during hypercalcemia (table 1). In two dogs with the highest recorded plasma concentrations of verapamil of 936 to 2043, ng/ml respectively, the AV block was more advanced than 2:1. This block was unchanged after the CaCl₂ infusion, as well as after the subsequent NaCl injection.

Figure 4. Effects of verapamil alone, after CaCl₂, and after CaCl₂ administration on the percent change of PP interval from control during sinus rhythm. Vertical bars are the average values and the vertical lines at their tops, ± SEM. The numbers of dogs (N) are shown under each bar. Statistical significance of p₁ relates to the comparison between values in the first bar vs those in other bars. Statistical significance of p₂ relates to the comparison between values in the third vs those in the fourth bar. Serum calcium concentrations are as in figure 1.

Sinus Rate and Rhythm in Verapamil-treated Dogs

At the verapamil concentrations of 70–480 ng/ml, the PP interval during sinus rhythm increased by an average of 34% in 24 dogs (fig. 4). Figure 4 shows that the PP interval did not change significantly after 5 and 15 minutes of CaCl₂ infusion. However, after the subsequent NaCl injection, PP interval decreased significantly to a value which was 19% greater than the control PP interval. This shortening of PP interval persisted for about 1 minute and could be reproduced by repeated injections of NaCl or Na lactate solutions, but not by sucrose. NaCl injections not preceded by CaCl₂ infusions had no effect on the PP intervals in four dogs at plasma verapamil concentrations of 100–270 ng/ml.

The two dogs whose plasma verapamil concentrations were 936 and 2043 ng/ml, respectively, had sinus
arrest. The arrest persisted after 15 minutes of CaCl₂ infusion and subsequent NaCl injection.

Sinus Rate in Dogs Not Treated with Verapamil

Administration of NaCl or Na lactate had no effect on PP intervals before or after CaCl₂ infusions. PP interval did not change after administration of CaCl₂ for 15 minutes, but became longer after longer CaCl₂ infusions associated with higher [Ca]₀. Figure 3 shows an experiment in which PP interval increased when [Ca]₀ reached 10.5 mEq/l. In three other experiments, the onset of increase in PP interval occurred at [Ca]₀ 10.1, 11.3, and 11.8 mEq/l.

Cardiac Output, Left Ventricular dp/dt, Aortic Pressure and Peripheral Vascular Resistance in Verapamil-treated Dogs

Cardiac output and left ventricular dp/dt increased in all dogs after 5 minutes of CaCl₂ infusion at plasma verapamil concentrations varying from 150-2042 ng/ml. Figure 5 shows that verapamil alone decreased cardiac output in seven of eight dogs, and that increase of [Ca]₀ from 4.6 ± 0.2 to 6.5 ± 0.3 reversed this effect and increased cardiac output to the levels which were higher than those before verapamil administration. Figure 6 shows similar effects on the left ventricular dp/dt which was depressed by verapamil, but after 5 minutes of CaCl₂ infusion returned to control levels or higher.

CaCl₂ administration increased, but did not reverse the verapamil-induced decrease in mean aortic pressure (fig. 7). Figure 7 shows that the peripheral vascular resistance (PVR) decreased after CaCl₂ administration, because the increase of cardiac output exceeded the increase in mean aortic pressure.

We found marked differences in the reversibility of certain hemodynamic and electrophysiologic effects of verapamil. These differences could not be attributed to differences in plasma verapamil concentration, because they were present when the hemodynamic and electrophysiologic effects were recorded simultaneously. Figure 8 shows an example of such an experiment. In the experiment shown in this figure, the verapamil-induced prolongation of AH interval remained unchanged when [Ca]₀ increased from 4.9 to 6.6 mEq/l (B, C), but decreased by 30 msec when [Ca]₀ reached 8.1 mEq/l. In contrast to this slow and incomplete reversal of AH prolongation, cardiac output and left ventricular dp/dt increased to values higher than control at [Ca]₀ of 6.6 mEq/l (C); they increased further at [Ca]₀ of 8.1 mEq/l (D). Figure 8 shows also that CaCl₂ infusion increased, but did not restore to control the systolic and diastolic aortic pressure.

Discussion

We previously reported the hemodynamic and electrophysiologic verapamil effects described in the dogs used in this study. The results of the present study are: 1) an increase of [Ca]₀ by 1-2 mEq/l reversed the negative inotropic effect of verapamil, but had no effect on AV conduction and sinus rate; 2) a greater increase in [Ca]₀ reversed, in part, the effects of verapamil on AV conduction, but not on sinus rate; 3) a rapid increase in [Na]₀ concentration reversed partially the verapamil effects on both AV conduction and sinus rate, but only after a prior increase in [Ca]₀; 4) severe depression of AV conduction and SA node function was irreversible, but severe depression of cardiac output and left ventricular dp/dt was reversible; and 5) AV conduction became slower and sinus rate decreased after a certain critical increase in [Ca]₀ in the absence of verapamil.

Our understanding of these phenomena is very limited because of many unanswered questions concerning the sites of verapamil action and the
mechanism of its interaction with Ca\textsuperscript{++} and Na\textsuperscript{+} at the cellular and subcellular level.

**Inotropic Effects**

Verapamil decreased the steady-state isotonic contraction force in the isolated cat papillary muscle.\textsuperscript{5} This effect was caused primarily by the (−) optical isomer of the drug.\textsuperscript{7} The negative inotropic effect appeared to be caused, at least in part, by blocking of the slow inward current.\textsuperscript{5} Kohlhardt et al. showed that a fourfold increase of Ca\textsuperscript{++} concentration in the bath neutralized or even overcompensated the effects of verapamil on the slow current and contractility.\textsuperscript{5} However, the studies of Bayer et al.\textsuperscript{5,7} revealed more complex interaction between verapamil and calcium. These investigators found that within the range of 6–60 Hz the negative inotropic effect of verapamil depended on the frequency of stimulation being more pronounced at higher than at lower stimulation rates. Thus, a three-fold increase in Ca\textsuperscript{++} concentration restored or overcompensated the verapamil-depressed steady-state isotonic contraction force at slow, but not at rapid rates of stimulation.\textsuperscript{5} This may be explained by the observations of Kohlhardt et al.\textsuperscript{5} that verapamil not only decreases the steady-state slow current, but also slows the recovery rate of this current.\textsuperscript{5} However, other manifestations of the verapamil-calcium interaction were less readily explained by the effect of the drug on the slow inward current. Thus, at a verapamil concentration of 5 ng/ml and a Ca\textsuperscript{++} concentration of 2.5 mM/l, an abrupt change in the stimulation rate from 60 to 6 Hz resulted in an overshoot of the increase in contractile force.\textsuperscript{5} We attributed this phenomenon to the possible action of verapamil on some intracellular time-dependent sites believed to be responsible for the kinetics of Ca\textsuperscript{++} movement from the sarcoplasmic reticulum to the "storage sites" in the lateral cisterns.\textsuperscript{5}

The detailed studies by Bristow et al. in the isolated rabbit atrium on the dose-response relationships of different verapamil and D600 (the methoxyderivative of verapamil) concentrations within a wide range of Ca\textsuperscript{++} concentrations suggested a competitive antagonism between these drugs and calcium on the dp/dt.\textsuperscript{10} However, unlike the compound D600, verapamil did not meet rigid criteria for the competitive antagonism, since the relative amount of antagonism decreased with increasing verapamil doses.\textsuperscript{10} Therefore, we have suggested that a "pharmacologic
property of verapamil unrelated to calcium antagonism leads to an increase of the availability of intracellular Ca++.

Our findings suggest that relatively small amounts of calcium are required to overcome the negative inotropic effect of therapeutic and toxic doses of verapamil. The practical application of these results to verapamil therapy in man must await the appropriate clinical studies. In our study the reversibility of the depressed left ventricular dp/dt persisted until the termination of the experiments, i.e., for not less than 45 minutes after the end of calcium infusion. In other studies the positive inotropic effects of intravenously administered calcium salts in intact animal and man usually lasted less than 15 minutes. This observation appears to favor the mechanism of competitive inhibition of verapamil effect by Ca++ rather than a non-specific positive inotropic effect of increased (Ca).

We found that increase in (Ca) increased cardiac output but lowered PVR. These effects of increased (Ca) concentration would be expected even in the absence of verapamil. Stanley et al. reported that 10 mg/kg of CaCl2 decreased the PVR in unanesthetized calves not treated with verapamil by an average of 19%. In our study, 15 mg/kg of CaCl2 decreased the verapamil-depressed PVR by an additional 10%. In the absence of control studies, we do not know if the effects of calcium on PVR were influenced by pretreatment with verapamil, but our results show that Ca++ does not reverse the verapamil-induced decrease in PVR. This suggests that the verapamil-calcium interaction in the smooth muscle may differ, at least quantitatively, from that in the cardiac muscle. Such differences are plausible, since Chiarandini and Bentley reported that in the skeletal muscle an increase in extracellular Ca++ concentration did not reverse the verapamil-induced inhibition of the Solandt effect and of the acetylcholine-induced contracture.

Effects on AV Conduction and Sinus Rhythm

We found that an increase of (Ca) to an average of 7.9 mEq/l caused a modest but significant decrease in the AH interval, but no change in the sinus rate. This suggests some antagonism of Ca++ and verapamil within the AV node, a finding not reported by previous investigators. Zipes and Fischer could not reverse verapamil effects by infusing calcium gluconate, CaCl2 and saline into arteries supplying the AV node and the SA node, respectively. The differences between our results and those of Zipes and Fischer may be caused by the doses and the methods of calcium administration. Dogs may tolerate intravenous better than intra-arterial calcium administration since the latter produced atrial or ventricular fibrillation, while we did not observe serious arrhythmias after intravenous CaCl2 administration.

The non-reversibility of sinus bradycardia induced by verapamil can be explained by the studies of Kohlhardt et al. on the rabbit SA node. They reported that a threefold increase in extracellular Ca++ concentration did not change the verapamil-induced depression of action potential overshoot, upstroke velocity and conduction block, and contrasted this lack of calcium effect on the SA node, with the reversibility of verapamil-induced depression of contractility in the ventricular myocardium. They also noted that the lack of Ca++ excess action on the SA node was not due to an irreversible damage of the node, because the drug effect could be washed out, and postulated the presence of unidentified differences between properties of the slow membrane channel in pacemaker cells and ventricular myocardium.

The failure of hypernatremia to affect the verapamil-induced changes on the AH interval was surprising for two reasons: 1) The inward Na+ current is believed to participate in the depolarization of the AV nodal fibers through both the rapid and the slow channel; therefore, high Na+ concentrations would be expected to improve conduction by influencing one or both of these mechanisms; 2) Watanabe reported that verapamil-induced AV block in the isolated rabbit hearts could be abolished by increasing the extracellular Na+ concentration from 145 to 172 mEq/l. The ineffectiveness of hypernatremia in our experiments could be due to an insufficient increase in Na+ concentration, or to an insufficient duration of high Na+ action. Unfortunately, we could not examine the effects of larger volumes of hypertonic Na+ solutions because they caused atrial fibrillation.

Effect of Hypernatremia in the Presence of Hypercalcemia

We found that NaCl and Na lactate injections significantly decreased the AH interval and increased the sinus rate in the verapamil-treated animals only after a previous CaCl2 infusion. It appears, therefore, that the action of Na+ may require some prior calcium-verapamil interaction. Further studies must clarify the mechanism of this phenomenon and establish its practical applicability in the treatment of verapamil toxicity.

Effects of Calcium on AV Nodal Conduction and Sinus Rhythm in the Absence of Verapamil

Our study confirmed the previously reported prolongation of PR interval and slowing of sinus rate in animals and in man with hypercalcemia. The effects of verapamil-calcium interaction in this study were confined to (Ca) concentrations that were lower than those which had independent effect on the AH interval and the sinus rate. However, higher Ca++ concentration may be expected to have a synergistic effect with verapamil on the AV nodal conduction and the sinus rate.

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